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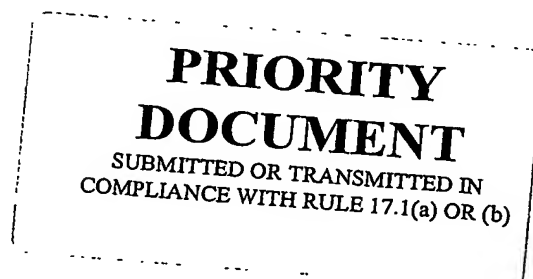
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02000288.7



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Pantoprazole Cyclodextrin Inclusion Complexes

15. Jan. 2002

Technical field

The present invention relates to the field of pharmaceutical technology and describes pantoprazole cyclodextrin inclusion complexes.

Background art

H⁺/K⁺-ATPase inhibitors, in particular pyridin-2-ylmethylsulfinyl-1H-benzimidazoles like those disclosed, for example, in EP-A-0 005 129, EP-A-0 166 287, EP-A-0 174 726 and EP-A-0 268 956 are important in the therapy of disorders originating from increased gastric acid secretion. Examples of active ingredients from this group which are commercially available are 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: omeprazole), 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: pantoprazole), 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: lansoprazole) and 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl]-1H-benzimidazole (INN: rabeprazole).

WO86/00913 discloses to form a stable complex by mixing and reacting omeprazole with β -cyclodextrin in 96% ethanol and cooling the reactant. WO93/13138 is related to a method for preparing enteric coated oral drugs containing acid-unstable compound, in particular an enteric-coated oral drug prepared in the form of acid-stable dosage unit inclusion complex formed by reacting benzimidazole derivative, acid-unstable compound, with cyclodextrin in alkaline solution. WO9638175 is related to a stabilized composition comprising an antiulcerative benzimidazole compound, particularly a proton pump inhibitor and a branched cyclodextrinic carboxylic acid.

Description of the invention

Surprisingly it has now been found that by reaction of pantoprazole with a cyclodextrin, inclusion complexes are obtained with increased overall solubility for pantoprazole brought about by the formation of soluble pantoprazole-cyclodextrin complexes.

Subject of the present invention is a pantoprazole cyclodextrin inclusion complex.

Pantoprazole in connection with the invention refers to 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole. Pantoprazole is a chiral compound. The term pantoprazole in connection with the invention also encompasses the pure enantiomers of pantoprazole and their

mixtures in any mixing ratio. Pure enantiomers which may be mentioned by way of example are (-)-pantoprazole and (+)-pantoprazole. Pantoprazole may be present as such or, preferably, in the form of its salts with bases. Examples of salts with bases which may be mentioned are sodium, potassium, magnesium or calcium salts. If pantoprazole is isolated in crystalline form, it may contain variable amounts of solvent. The term pantoprazole therefore also represents according to the invention all solvates, in particular all hydrates, of pantoprazole and its salts.

In a preferred embodiment pantoprazole refers to pantoprazole sodium sesquihydrate (= pantoprazole sodium x 1.5 H₂O), (-)-pantoprazole sodium sesquihydrate or pantoprazole magnesium dihydrate.

Cyclodextrin in connection with the invention preferably refers to α -, β - or γ -cyclodextrin, mixtures of α -, β - or γ -cyclodextrin or derivatives of α -, β - or γ -cyclodextrin. In a preferred embodiment of the invention cyclodextrin refers to β -cyclodextrin or hydroxyethyl- β -cyclodextrin.

The pantoprazole cyclodextrin inclusion complexes may be produced for example by standard procedures for preparation of compound-cyclodextrin inclusion complexes. Such procedures are for example disclosed in WO86/00913, WO93/13138, WO9638175 or by Duchene (in Proceedings of the Fourth International Symposium on Cyclodextrines, 265-275, 1988 by Kluwer Academic Publishers; eds. O. Huber and J. Szejtli). Inclusion compounds are usually prepared in liquid medium, but they can also be obtained in the solid phase, or by a kneading method. In one embodiment of the invention the inclusion complex is obtained by reacting pantoprazole with the cyclodextrin in a suitable solvent. In a preferred embodiment of the invention the solvent is an aqueous solvent or a solvent which essentially consists of an aliphatic alcohol, preferably ethanol. The inclusion complex may then be obtained by precipitation or freeze drying. In one embodiment the inclusion complex is obtained according to the method described in WO86/00913.

The pantoprazole cyclodextrin inclusion complexes of the invention can then be used as a basis for the production of the administration forms according to the invention. Administration forms according to the invention which may be mentioned, to which the preparations can be processed, are, for example, suspensions, gels, tablets, coated tablets, multicomponent tablets, effervescent tablets, rapidly disintegrating tablets, powders in sachets, sugar-coated tablets, capsules or alternatively suppositories. The excipients which are suitable for the desired administration forms are familiar to the person skilled in the art on the basis of his/her expert knowledge. Due to the increased solubility of pantoprazole in the pantoprazole cyclodextrin inclusion complex administration forms containing such inclusion complex have improved active compound bioavailability properties.

Suitable administration forms are for example disclosed in WO9222284, WO9702020,

EP-A-0 244 380, WO96/01623, WO96/01624, WO96/01625 or WO97/25030.

The administration forms according to the invention comprise the pantoprazole or pantoprazole cyclodextrin inclusion complex in the dose customary for the treatment of the particular disorder. The pantoprazole cyclodextrin inclusion complex of the invention can be employed for the treatment and prevention of all disorders which are regarded as treatable or preventable by the use of pyridin-2-ylmethylsulfinyl-1H-benzimidazoles. In particular, the pantoprazole cyclodextrin inclusion complex of the invention can be employed for the treatment of gastric disorders. Administration forms such as tablets contain between 1 and 500 mg, preferably between 5 and 60 mg, of an acid-labile proton pump inhibitor. Examples which may be mentioned are tablets which contain 10, 20, 40 or 50 mg of pantoprazole. The daily dose (e.g. 40 mg of active ingredient) can be administered, for example, in the form of a single dose or by means of a plurality of doses of the tablets of the invention (e.g. 2 x 20 mg of active ingredient).

EXAMPLE**5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole sodium sesquihydrate β -cyclodextrin inclusion complex**

1.73 g of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole sodium sesquihydrate, 5.67 g β -cyclodextrin and 20 ml of ethanol (96%) are heated to 30 to 32° C and stirred for 15 hours. The mixture is cooled to 10 ° C within 3 hours, filtered and the precipitate washed with ethanol (10 ° C). After drying under reduced pressure the title compound is obtained.

COMPLEXATION STUDIES OF PANTOPRAZOLE WITH CYCLODEXTRINS

Methods: Various solutions of the different cyclodextrins taken into consideration were prepared in phosphate buffer solution pH 7 at known concentrations and used to create saturated solutions of pantoprazole. After equilibration, these saturated solutions were filtered through MFTM membrane filters (pore size 0.45µm), appropriately diluted with phosphate buffer solution and subjected to uv/vis spectrophotometric analysis. The cyclodextrin solutions prepared with phosphate buffer ranged from concentrations of 0% p/v up to 1.8% p/v for βCD, 20% p/v for HPβCD.

Results: In both cases, the solubility of pantoprazole increased markedly with increasing cyclodextrin concentration. In the presence of βCD pantoprazole's solubility rose to a four fold maximum with respect to its solubility in phosphate buffer whereas when equilibrated with HPβCD, pantoprazole showed an outstanding increase in its solubility reaching over seventy times that in phosphate buffer solution.

Conclusions: The phase solubility studies with βCD and HPβCD were both characterised by an overall increase in pantoprazole's solubility brought about by the formation of soluble pantoprazole/cyclodextrin complexes. In the case of βCD phase solubility studies, the increase observed followed a typical A_p pattern commonly described by Higuchi-Connor, indicating the formation of complexes with an order higher than one. Pantoprazole's behaviour with HPβCD also followed a typical Higuchi- Connor's A_p pattern characterised further by an initially gradual increase in solubility.

15. Jan. 2002

Claims

1. Inclusion complex formed of pantoprazole, a salt of pantoprazole with a base, an enantiomer of pantoprazole or a salt of an enantiomer of pantoprazole and cyclodextrin.
2. Inclusion complex according to claim 1 formed of pantoprazole sodium sesquihydrate (= pantoprazole sodium x 1.5 H₂O), (-)-pantoprazole sodium sesquihydrate, pantoprazole magnesium dihydrate.
3. Inclusion complex according to claim 1 or 2, wherein the cyclodextrin is β -cyclodextrin.
4. Method for preparation of an inclusion complex according to any of claims 1 to 3 by reacting pantoprazole with the cyclodextrin in a suitable solvent.
5. Method according to claim 4, wherein the solvent is essentially ethanol.
6. Inclusion complex obtainable according to claim 4.
7. Administration form comprising an inclusion complex according to any of claims 1 to 3 together with suitable pharmaceutical auxiliaries.
8. Inclusion complex according to any of claims 1 to 3 for the treatment or prophylaxis of diseases of disorders originating from increased gastric acid secretion.

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Abstract

An inclusion complex formed from pantoprazole and cyclodextrin is described.

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